REMARKS

The amendments to the specification find support in the application as filed. A new paragraph beginning at page 1, line 11 has been added in the specification. The new paragraph lists the applications to which priority is claimed for the instant application. Applicants note that these amendments to the specification are similar to amendments made in the parent application of the present application. These changes are of formal nature; no new matter is added to the specification by way of the amendments.

For example, (1) original figures 1 and 2 have been amended to clearly identify the two separate sequences shown as "1A", "1B", and "2A" and "2B", respectively. Corresponding amendments have been made in the legends of Figures 1 and 2; (2) a substitute Figure 4 is submitted that contains an explanation of each symbol used in the schematic representation of the trks and their alternate splice forms and their domains; (3) the legend of Figure 4 has been amended to better describe Figure 4 by defining the meaning of the triangles, which represent optionally present peptide inserts. Additionally, various typographical errors in the specification have been corrected.

Support for these amendments are found in the specification at page 17, line 1 to page 18, line 8, where the trk domains are described, in the detailed description of the trk's and their alternate splicing forms at pages 97-103, in the Examples at page 98, lines 22-28, where the 6 amino acid peptide insert into trk A is described by means of its nucleic acid sequence, and in the description of the non-human trkB isoform at page 98, line 30 to page 99, line 11.

In order to ensure conformity with the Sequence Listing submitted concurrently herewith, amendments to the specification have been made to reflect the new SEQ ID NO:s in this Sequence Listing. The Sequence Listing is believed to better organize the sequences than the original SEQ ID NO:s. For the Examiner's convenience, a brief explanation of the SEQ ID NO: change follows: SEQ ID NO: 1 remains the nucleic acid sequence for a full-length human trkB; however, SEQ ID NO:2 is now the translated amino acid sequence of SEQ ID NO:1. SEQ ID NO: 3 is a truncated human trkB nucleic acid sequence, and SEQ ID NO: 4 is its corresponding

translated amino acid sequence, which finds support in Figure 1B and in the detailed description of this splice form in the specification. SEQ ID NO: 5 is a full-length human trkC nucleic acid sequence (originally SEQ ID NO: 2), and SEQ ID NO: 6 is its corresponding translated amino acid sequence, which is also supported in Figure 2A. SEQ ID NO: 7 is a truncated human trkC nucleic acid sequence, and SEQ ID NO: 8 is its corresponding amino acid sequence, which finds support in Figure 2B and in the detailed description of this splice form in the specification. SEQ ID NO:9 is a full-length human trkA amino acid sequence, which is found in Figure 16. SEQ ID NOs: 10 through 35 are nucleic acid sequences for the oligonucleotides found in Table 1. SEQ ID NO: 36 is amino acid sequence ESTDNFILF, which is bracketed in Figure 2A. SEQ ID NO: 37 is amino acid sequence LFNPSGNDFCIWCE, which is also bracketed in Figure 2A. SEQ ID NO: 38 is the nucleic acid sequence TCTCCTCTCGCCGGTGG and SEQ ID NO: 39 is its corresponding translated 6 amino acid peptide Ser-Pro-Ser-Arg-Trp, which are supported at least at page 98, line 26. Finally, SEQ ID NO: 40 is the amino acid sequence FVLFHKIPLDG from Figure 1B, which is the trkB alternate C-terminal sequence, and SEQ ID NO: 41 is the amino acid sequence from Figure 2B which represents the trkC alternate C-terminal sequence.

Claims 6-12 are pending in the application and stand amended. The amendments to claim 6 find support in the specification, for example, at page 10, lines 20-25; page 15, lines 30-31; and elsewhere in the application. The amendments to claims 7-12 correct the dependency of the claims.

No new matter is added by way of the claim amendments.

The Examiner has not considered the information disclosure statement filed with the application on October 31, 2003.

The Examiner has not accepted that the parent applications establish the priority date of the present application. The Examiner has not accepted the Declaration filed for the parent applications as sufficient for the present application.

The specification stands objected to as allegedly being unclear with regard to figure legends for Figures 1 and 4, and also as allegedly failing to provide proper antecedent basis for the claimed subject matter.

Pursuant to a Restriction Requirement, claims 6-9 and 12 with regard to "a method for diagnosing malignancy or tumor, by detecting the human trkB receptor bound to NT-4 or NT-4/5" were examined in the application.

Claims 7-9 and 12 stand objected to for depending on non-elected claims 20-21. Claims 6-9 and 12 stand rejected as allegedly being indefinite, as allegedly failing to comply with the written description requirement, and as allegedly failing to comply with the enablement requirement.

Applicants respectfully submit that the parent applications provide support for, and establish the priority date for, the present application; respectfully submit that the original Declaration is sufficient for the present application; and traverse the objections and rejections as discussed below.

The Information Disclosure Statement

Applicants re-submit the Information Disclosure Statement (IDS) noting on the IDS that it pertains to the present application, although derived from IDSs filed with regard to parent applications.

The Priority Date

The Examiner has established the filing date of this continuation application as the priority date for the claimed subject matter. Applicants note that support for all claims in the application, including claims 6-9 and 12, is found in all parent applications.

For example, support for claims 6-12 is found in the earliest-filed parent application, SN 08/215,139 at page 5, lines 15-24; page 10, lines 14-19; page 80, lines 10-20 and 29-31; page 86, lines 22-30; page 88, lines 1-14; and elsewhere in that application as filed on March 18, 1994.

In particular, support for claim 6 is found in SN 08/215,139 at page 5, lines 15-24; page 10, lines 14-19, and elsewhere in the application as filed.

Support for claim 7 is found in SN 08/215,139 at page 5, lines 10-11, and elsewhere in the application as filed.

Support for claim 8 is found in SN 08/215,139 at page 88, line 5, and elsewhere in the application as filed.

Support for claim 9 is found in SN 08/215,139 at page 88, line 3, and elsewhere in the application as filed.

Support for claim 10 is found in SN 08/215,139 at page 88, line 6, and elsewhere in the application as filed.

Support for claim 11 is found in SN 08/215,139 at page 88, line 6, and elsewhere in the application as filed.

Support for claim 12 is found in SN 08/215,139 at page 2, lines 21-28, page 15, lines 18-23, and elsewhere in the application as filed.

Thus, Applicants submit that the present application is entitled to the priority date of March 18, 1994, the date on which the earliest-filed parent application, SN 08/215,139, was filed.

The Oath or Declaration

The Examiner has required a new Oath or Declaration, suggesting that the application "seems to be a continuation-in-part and not a divisional of the patent applications." However, as noted above, the present claims all find support in all the parent applications, including the initial application, and so are entitled to the earliest filing date of the parent applications.

Applicants further note that the Restriction Requirement mailed October 3, 1994 with regard to the original parent application included Group VII, claim 40, directed to "a method for the diagnosis of a pathological condition characterized by over- or underexpression of a neurotrophic factor." Thus, the present application is related to the original parent application as a divisional application, and not as a continuation-in-part.

Since the subject matter of the claims was disclosed in the original application, and since a declaration signed by the inventors was filed with the original application, it is believed that no new or additional oath or declaration is needed.

The Specification

The figure legend for Figure 1 on page 11 stands objected to as allegedly unclear as to what the amino acid sequence and nucleotide sequence of the truncated form of trkB are attached to. As amended, the figure legends for Figure 1 and Figure 2 no longer use the word "attached" to indicate that a sequence listing is provided with the specification, instead noting that the sequences are "disclosed in" the named sequence listings. Accordingly, the figure legend for Figure 1 is believed to be clear.

The amendment to the specification filed on October 31, 2003 was not entered for alleged lack of clarity, the Examiner objecting to the discussion relating to the closed triangle, the half-closed triangle, and the smaller and larger open triangles of Figure 4. As amended, the figure legend for Figure 4 refers to the triangles in the figure by location and size, and does not refer to the triangles as "closed," "half-closed," or "open." Accordingly, the amendments to the legend for Figure 4 are believed to be clear.

The specification also stands objected to as allegedly failing to provide proper antecedent basis for the claimed subject matter. However, as noted above, support for the claimed subject matter may be found in the earliest of the parent applications, and, as noted in the Preliminary Amendment filed on October 31, 2003, support for the pending claims may be found in the present application at page 5, lines 26-32 and at page 91, lines 6-20 (claim 6); page 5, lines 17-19 and page 91, line 11 (claim 7); page 5, lines 17-19, and page 10, lines 20-25 (claim 8); page 91, line 9 (claim 9); page 9, line 12 (claim 10); page 91, lines 12-13 (claim 11); and page 4, line 10 (claim 12).

Accordingly, Applicants believe that the objections to the specification are overcome.

The Objections to Claims 7-9 and 12

Claims 7-9 and 12 stand objected to as depending upon non-elected claims 20-21. As amended, claims 7-9 and 12 depend from claim 6 or 7 of the present application. Accordingly, Applicants believe the objections to claims 7-9 and 12 to be overcome.

The Rejections of Claims 6-9 and 12 under 35 U.S.C. § 112, Second Paragraph

Claims 6-9 and 12 stand rejected, the Examiner objecting to the term "said neurotrophic factor."

Antecedent basis for the term "said neurotrophic factor" is provided by the amendment to claim 6 amending the term "neurotrophin" to be "neurotrophic factor." Applicants note that the specification defines the terms "neurotrophin" and "neurotrophic factor" to be interchangeable (see, e.g., page 15, lines 30-31). Accordingly, Applicants believe the claims to be definite, and the rejections of claim 6-9 and 12 under 35 U.S.C. § 112, second paragraph to be overcome.

The Rejections of Claims 6-9 and 12 under 35 U.S.C. § 112, First Paragraph, Written Description

Claims 6-9 and 12 stand rejected as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner notes that the term "trkB" cited in claim 6 is not accompanied by a sequence identification number, and cites University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. v. Gen-Probe Inc (285 F.3d 1013, 62 U.S.P.Q.2d 1289 (Fed. Cir. 2002)) to suggest that "the specification does not describe the human trkB receptor, and the neurotrophic factor NT-4, or NT-4/5 in a manner that satisfies either the standards as shown in the example of Lilly or Enzo" (page 11, lines 3-5 of the Office Action mailed October 24, 2006). While acknowledging that "the specification discloses a single human trkB receptor, SEQ ID NO:2, and its spliced variant SEQ ID NO:40," the Examiner further suggests that "this does not provide a description of the human trkB receptor, and the neurotrophic factor NT-4, or NT-4/5 that would satisfy the standard as shown in the example of Enzo" (page 11, lines 9-12 of the Office Action mailed October 24, 2006). The Examiner thus concludes that "[t]he specification does not provide an adequate written description of the human trkB receptor, and the neurotrophic factor NT-4, or NT-4/5 that is required to practice the claimed invention" (page 11, lines 19-21 of the Office Action mailed October 24, 2006).

However, as discussed below, the cited cases are not properly applicable to these claims, and there is adequate support for the claimed methods in the specification.

The Legal Standard

Applicant notes that the Federal Circuit stated that "it is the binding precedent of this court that *Eli Lilly* does *not* set forth a *per se* rule that whenever a claim limitation is directed to a macromolecular sequence, the specification must always recite the gene or sequence, regardless of whether it is known in the prior art." Falkner v. Inglis, 79 USPQ2d 1001, 1008 (Fed. Cir. 2006). Moreover, the Federal Circuit, in Falkner v. Inglis, held that "where ... accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences (here, "essential genes"), satisfaction of the written description requirement does not require either the recitation or incorporation by reference of such genes and sequences" Id. at 1008-1009, and that "there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." Id. at 1007.

Thus, the cases cited by the Examiner do not serve to require that verbatim sequences be provided in a specification in order to satisfy the written description requirement. As stated by the Federal Circuit in Falkner v. Inglis "[t]he 'written description' requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way." Id. at 1008.

Support in the Specification

Applicant notes that the specification clearly discloses that the scientific literature provided substantial description, including sequences, of the neurotrophins NT-4 and NT-4/5 (see, e.g., page 2, lines 31-33 to page 3, lines 1-5, and elsewhere in the specification). Thus, one of ordinary skill in the art would know how to identify and how to use the neurotrophins NT-4 and NT-4/5 as required in the claims. As acknowledged by the Examiner, sequences of human trkB receptor and a splice variant of a human trkB receptor are disclosed in the application. Further discussion of splice variants and other variant trkB receptors is provided in the application (see, e.g., Figures 1, 3, 4, and 16; pages 39-44; 58-65; 94-96; and elsewhere in the application). In addition, the specification provides discussion, disclosure and identification of

literature describing various non-human trkB receptors (see, e.g., page 3, lines 20-33 though page 4 to page 5, line 21). Thus, the disclosure of the application and the knowledge of one of ordinary skill in the art, in view of the teachings provided by the Applicants in the application, provide sufficient written description to show that the Applicants had possession of the claimed invention.

Accordingly, Applicants submit that the rejections of claim 6-9, and 12 under 35 U.S.C. § 112, first paragraph, written description, are overcome.

The Rejections of Claims 6-9 and 12 under 35 U.S.C. § 112, First Paragraph, Enablement

The Wands Factors

Claims 6-9, and 12 stand rejected under 35 U.S.C. § 112, First Paragraph, as allegedly failing to comply with the enablement requirement, the Examiner listing some considerations with respect to the factors enumerated in *In re Wands* (8 USPQ2d 1400 (Fed. Cir. 1988)). These factors are discussed in the following paragraphs.

Applying the *In re Wands* factors to the present claims, we find that:

1) The nature of the invention:

The claims are drawn to methods for diagnosis of pathological conditions. The Examiner suggests that this invention is complex (page 13, lines 2-6 of the Office Action mailed October 24, 2006). However, applicants submit that the claimed methods, all requiring that the condition to be diagnosed be one of over- or underexpression of a neurotrophic factor, and all requiring the same steps of contacting a sample and of detecting the presence of the neurotrophic factor, are not complex since they all share the same, few steps.

The claimed methods include steps of *contacting* and *detecting*. Contacting a biological sample with a labeled receptor is routine in the art. Detecting binding of a probe with a target, or a ligand with a receptor, is also routine in the art. Thus, the nature of the claimed invention is routine in the art.

2) The state of the prior art:

As acknowledged by the Examiner, the closest prior art fails to teach detection of NT-4 using human trkB receptor (page 17, line 18 of the Office Action mailed October 24, 2006).

3) The relative skill of those in the art:

As acknowledged by the Examiner, the relative skill of those in the art is high. Applicants do not believe that undue experimentation would be required to practice the invention (as suggested by the Examiner on page 13, lines 13-14 of the Office Action mailed October 24, 2006), since detection of labeled polypeptides is well-known and routine in the art, and since the specification provides detailed explanation and examples related to the claimed methods (see, e.g., pages 79-81; 86-90, particularly 86-87; and elsewhere in the application).

4) The predictability or unpredictability of the art:

The Examiner suggests that "one cannot predict which of the claimed numerous pathological conditions, cancers, abnormal growths, or pancreatic disorders actually produce NT-4 or NT-4/5" and that the structure and function of the encompassed variant human trkB receptors, and variant neurotrophins NT-4 or NT-4/5 cannot be predicted, in view of the unpredictability of protein chemistry" (pages 13-14 of the Office Action mailed October 24, 2006). The Examiner cites references suggesting that different neurotrophic factors may be expressed in different diseases, and that the binding properties of variant receptors may be unknown, given that proteins may be sensitive to "alterations of even a single amino acid" (page 15 of the Office Action mailed October 24, 2006).

However, Applicants note that the claims require that, in the condition to be diagnosed by the claimed methods, a neurotrophic factor capable of binding a human trkB receptor be over- or underexpressed. Thus, Applicants submit that the Examiner's concerns regarding binding, or expression, are moot since the claims only refer to those conditions, neurotrophic factors, and receptors where over- or underexpression occurs, and where the neurotrophic factors are indeed capable of binding to the receptors.

Moreover, Applicants submit that the predictability of biotechnological arts is high where specific sequences are known in the art, in that methods for producing proteins and nucleic acids

of known sequence are well-known and predictable, and that methods for producing desired variants of such sequences are also well-known and predictable.

5) The breadth of the claims:

The Examiner suggests that the claims are broad (page 12, lines 16-20 of the Office Action mailed October 24, 2006). However, as amended, the claims require that the pathological condition to be diagnosed be one that is "characterized by the over- or underexpression of a neurotrophic factor" and is thus limited to those conditions having that identified characteristic. The fact that such conditions may include the named particular manifestations, such as a malignancy (claim 7), or a tumor (claim 8), or a pancreatic disorder (claim 9), does not increase the breadth of the claim, as all the claims are limited to methods related to disorders with the named characteristic (over- or underexpression of a neurotrophic factor). Thus, the claims are not broad in that the claimed subject matter is explicitly recited in the claims and limited to particular pathological conditions all exhibiting the named identifying characteristic.

6) The amount of direction or guidance provided, and

7) The presence or absence of working examples:

The Examiner notes that the application discloses the full-length and at least one truncated transcript of human trkB. In addition, the specification provides extensive teaching regarding how to make and use the receptors and neurotrophic factors. See, for example, pages 16-21; 31-45; 58-65; 86-87; and elsewhere in the application. The Examiner also notes the explicit disclosure of the detection of such transcripts in various human tissues.

However, the Examiner suggests that there is "no disclosure in the specification which pathological conditions, which cancers, which tumors, or which pancreatic disorders express the neurotrophin NT-4 or NT-4/5, or variants thereof, wherein said neurotrophin does not exist in the corresponding control sample, and wherein said neurotrophin could be detected by the human trkB receptor protein or a variant thereof" (Pages 15-16, Office Action mailed October 24, 2006). Applicants note that there is no limitation in the claims that "said neurotrophin does not exist in the corresponding control sample." In fact, the claims are directed to conditions in which the neurotrophic factor is "over- or underexpressed" which do not require that the neurotrophic

factor be absent from control samples. Moreover, the specification, and in addition the literature cited therein, teach that the human trkB receptor polypeptides bind neutrophic factors such as NT-4 and NT-4/5, and teaches tissue distributions of such receptors. These teachings, examples, methods and techniques enable one of ordinary skill in ways to practice the invention by directing that person to pathological conditions of those tissues and conditions.

8) The quantity of experimentation necessary:

As discussed above, the application and the knowledge of one of ordinary skill in the art allow one of ordinary skill in the art to perform the contacting step and the detecting step of the claimed methods, as is routine in the art. Thus, no more than a routine amount of experimentation would be required to practice the invention.

Accordingly, the analysis of the *In re Wands* factors indicating that the amount of experimentation required to practice the invention is not undue, Applicants submit that the claims are enabled and that the rejections of claims 6-9, and 12 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement are overcome.

The "essential materials"

Claims 6-9, and 12 also stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly requiring essential materials NT-4 and NT-4/5 "which are however only incorporated by reference to publications in the art" and the Examiner has required that the application be amended to disclose the material incorporated by reference (page 16, lines 18-22, Office Action mailed October 24, 2006).

However, Applicants note, as cited above, that the Federal Circuit has held that "where ... accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences (here, "essential genes"), satisfaction of the written description requirement does not require either the recitation or incorporation by reference of such genes and sequences" Falkner v. Inglis, at 1008-1009, and that "there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." Id. at 1007.

Accordingly, since these neurotrophic factors were known in the art, as evidenced by the citations to the literature recited in the application as filed, Applicants believe that the law does not require that the application be amended to recite the sequences of NT-4 or NT-4/5. Applicants submit that the rejections of claims 6-9, and 12 under 35 U.S.C. § 112, first paragraph as allegedly failing to recite essential materials are overcome.

CONCLUSION

Applicants respectfully submit that claims 6-9 and 12 are in condition for allowance, and respectfully request their allowance. In view of the allowable subject matter of the linking claim, claim 6, Applicants further request that the restriction requirement be withdrawn and that the remaining claims and subject matter be examined and allowed. Early notification of the allowance of the application is respectfully requested.

The Examiner is invited to contact the undersigned attorney at the telephone number indicated below should he find that there are any further issues outstanding.

Although no fees are believed to be due, please charge any fees to Deposit Account No. **08-1641 (Attorney's Docket No. 39766-0033 CP2C2C1)**.

Respectfully Submitted,

Date: December 1, 2006

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